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THE COUNCIL FOR TOBACCO RESEARCH-U.S.A., INC.

110 EAST 59TH STREET
NEW YORK, N.Y. 10022
(212) 421-8985

Application for Research Grant
(Use extra pages as needed)

Date: Jan. 24,
1974

JAN 31 1974

1. Principal Investigator (give title and degrees):

Thomas R. Dawber, M.D., M.P.H. Principal Investigator
H. Emerson Thomas, Jr., M.D. Co-Investigator
Carl C. Seltzer, Ph.D. Co-Investigator

2. Institution & address:

Boston University School of Medicine
80 East Concord Street
Boston, Ma. 02118

3. Department(s) where research will be done or collaboration provided:

Department of Medicine
Section on Preventive Medicine & Epidemiology
Evans Department of Medical Research

4. Short title of study:

Epidemiologic Study of Cigarette Smoking and Cardiovascular Disease

5. Proposed starting date: July 1, 1974

6. Estimated time to complete: Two years

7. Brief description of specific research aims:

To evaluate the effect of age on the relationship between cigarette smoking and coronary heart disease, stroke and peripheral vascular disease.

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8. Brief statement of working hypothesis:

The reported effect of cigarette smoking on the development of coronary heart disease, stroke and peripheral vascular disease is not one related to atherogenesis but to other factors which affect the development of an overt episode, e.g. thrombosis or arrhythmia.

Persons susceptible to these events develop them earlier if they smoke cigarettes. The net effect is to cause clinically overt disease to appear earlier in cigarette smokers than non-smokers. Ex-smokers will be at an even lower risk than those who never smoked. A third observation should be the disappearance of the effect of cigarette smoking with increasing age as susceptible persons are removed from the population.

If the above hypotheses are correct, our approach to the cigarette smoking risk insofar as coronary heart disease is concerned is development of practicable methods of detecting highly susceptible persons as early in life as possible.

9. Details of experimental design and procedures (append extra pages as necessary)

The proposed study is a continuation of existing investigations of risk factors and cardiovascular disease in the Framingham Study. In July 1971 a grant was awarded to the Boston University Medical Center by the Council for Tobacco Research to assist in the continuation of the Framingham Study. This longitudinal investigation of the epidemiology of coronary heart disease was begun in 1949 - 1950 by the National Heart and Lung Institute and has followed the original cohort population of 5,209 subjects selected in January 1950. This population aged 30 - 59 at the onset of the study is now 53 - 82. The population has decreased through death to 4,076 subjects as of Nov. 30, 1973.* At the time the NHLI first decided to phase out the study it was unclear exactly what was planned. Later when the Boston University Medical Center actively developed a program aimed at continuing the Study the NHLI decided to maintain surveillance of causes of death and to follow-up on such hospitalizations as were possible. Readily available was information from the local Framingham Union Hospital where the study was located. Information from other hospitals, however, usually depended on knowledge of an illness which could only be obtained from direct contact with the patient or an immediate relative.

In view of the NHLI decision to maintain a limited population surveillance in Framingham the task of the BUMC - Framingham Study was somewhat lessened, but the big task of direct examination of the available members of the cohort required a major effort. The BUMC - Framingham Study began in July 1971 to plan the twelfth re-examination of the population. This required development of new examination forms, recruitment of a staff to bring in subjects for examination, conduct the examinations, process the data, etc. All this was rapidly

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*see Appendix A

9. Details of experimental design and procedures (cont.)

accomplished and the Study was reactivated in September 1971. During the next two years the available population was re-examined for the twelfth time. This examination has been completed as of January 1, 1974.*

Meanwhile, Examination 13 was begun in September 1973, again to be conducted over a two-year period. Processing of the data collected at Exam 12 has been on-going during the examination period.

The availability from the NHLI of data previously collected in Framingham has been delayed by actions of that organization. This was done on the grounds that until the present BUMC - Framingham Study investigators had completed the examination of the cohort they did not have any need for previous data which belonged to the NHLI and the analysis of which was not a proper function of others than the NHLI investigators. This delay has made it impossible for the present investigators to carry out certain preliminary studies which they proposed in the previous grant application until past data could be acquired.

In view of the NHLI attitude the principal investigator sought certain data on his own initiative and has been able to put together sufficient information from previous examinations to make possible the analysis of data on smoking in relation to a number of disease end points and also to other factors of risk should the NHLI not see fit to provide the desired information.

Tapes covering data from the previous examinations at Framingham have now been received and constitute a better set than other data available. These data are for our use in analyzing data collected by us in the twelfth and subsequent examinations. Publication of reports covering the entire data is understood to be our prerogative.

In this regard the nature of the relationship between the current operation conducted by the NHLI in Framingham and the Boston University Medical Center - Framingham Study should be made clear. The NHLI is currently funding a follow-up of death and hospitalization of subjects in the Study while our activity involves a clinical appraisal of all living subjects. We also participate in the review and collection of the pertinent data in which the NHLI has a legitimate interest. We collaborate with the NHLI staff in conducting the entire study. This has included a number of scientific publications. Because the data in these

*See appendix B and C

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9. Details of experimental design and procedures (cont.)

has essentially all come from previous data collected by the NHLI such publications have needed approval from that organization.

Now that we have completed the twelfth examination and have received tapes on the past data a larger number of publications will result directly from our own group. Such reports will represent the opinions of our own investigators and not be subject to NHLI review. At the same time, publications will continue to be generated by the NHLI staff and, if involving data obtained by us, will be published as a joint project.

We currently have made a review of the number of disease endpoints which have been accumulated and will now be able to provide the investigators with data for the study of smoking in relation to coronary heart disease, stroke and peripheral arterial disease in twenty-two years of observation. This will enable us to determine what changes have taken place, if any, in the risk of those manifestations of cardiovascular disease with changes in age. Dr. Seltzer plans a study of the data pertaining to the predisposition of ^{smoking habits and} alcohol consumption and development of coronary heart disease. Data which he wishes should be in his hands sometime in February 1974.

One approach has been to determine the "immediate" risk of cigarette smoking over an arbitrarily selected period of time following the observations of smoking habits. This risk is determined for each age bracket. Current observations have been confined to myocardial infarction but steps have been taken to widen these to include the other manifestations of coronary disease, stroke and peripheral arterial disease.

In order to carry out this study it is necessary to know the current smoking status of all the subjects since this status is constantly changing. To obtain such information requires the kind of direct continued surveillance of the Framingham Study population which has been made possible by the Boston University Medical Center effort and for which funds have been contributed by foundations, the insurance industry, pharmaceutical firms and large numbers of private individuals, both participants and non-participants as well as by grant support from the N.I.H. and the Council for Tobacco Research.

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9. Details of experimental design and procedures (cont.)

From the data so obtained it then becomes possible to evaluate the "immediate" risk on the basis of known smoking status rather than on an assumption of unchanged smoking habits which has characterized reports from Framingham, i.e. based on the reported habits at the initial examination.

Preliminary observations (on which the attached abstract submitted for presentation of a paper on the subject at the next American College of Physicians meeting was based) indicate clearly that there is a decrease in risk of cigarette smoking insofar as myocardial infarction is concerned with increasing age beginning with the youngest subjects studied. This risk may be partially due to the failure to fully account for all subjects who have discontinued smoking but future analysis will take this into consideration. As the subjects reach the age of 60 - 70 the effect of cigarette smoking on myocardial infarction disappears and the trend suggests strongly that a reversal of the effect with a lesser risk in the smokers than in the non-smokers above this age.

Because of the relatively small number of older subjects there is a need for follow-up of the Framingham population for a few more years (two may be sufficient) to enable the suggested findings to be adequately confirmed.

The data from Exam 12 can now be added to the data from previous examinations and a number of reports can now be prepared. A grant for five years from the National Institute for Neurology and Stroke was provided in 1971. The present grant request is therefore made for a two-year period to run concurrently with the NIH grant to enable the BUMC - Framingham Study investigators to complete the task of examining the study population, analyzing data from the 12th and 13th examinations as well as from previously collected data and preparing the desired reports. The next two years will be utilized in reporting the findings from a total of 22 years of observation as well as continuing further study of the population.

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10. Space and facilities available (when elsewhere than item 2 indicates, state location):

Space and facilities available to the National Heart and Lung Institute in Framingham under an agreement with the Framingham Union Hospital have been utilized by the Boston University Medical Center - Framingham Study at no cost. It is anticipated that this agreement will continue but with some modification requiring the BUMC - Framingham Study to acquire some additional space by direct negotiation with the Framingham Union Hospital.

11. Additional facilities required:

Additional space requirements were anticipated last year due to a projected change in space utilization by the Framingham Union Hospital. That change has not as yet materialized but will certainly do so during the current year necessitating rental of the additional space during the coming year.

12. Biographical sketches of investigator(s) and other professional personnel (append):

13. Publications: (five most recent and pertinent of investigator(s); append list, and provide reprints if available).

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14. First year budget:

A. Salaries (give names or state "to be recruited")
 Professional (give % time of investigator(s)
 even if no salary requested)

	% time	Amount
Thomas R. Dawber, M.D., M.P.H.	40%	\$12,000
H. Emerson Thomas, Jr., M.D.	25%	6,000
Carl C. Seltzer, Ph.D.	20%	5,000
Philip A. Wolf, M. D.	--	--
Technical		
Clerk typist	100%	8,250
Statistical clerk	100%	8,250
		39,500
		Sub-Total for A

B. Consumable supplies (by major categories):

Record forms	500
Office supplies	500
	1,000
	Sub-Total for B

C. Other expenses (itemize):

Travel	1,500
Data processing	4,000
Space (40% of cost)	1,500
	7,000
	Sub-Total for C

Running Total of A + B + C

47,500

D. Permanent equipment (itemize):

Sub-Total for D	--
E	7,125
Total request	54,625

E. Indirect costs (15% of A+B+C)

15. Estimated future requirements:

	Salaries	Consumable Suppl.	Other Expenses	Permanent Equip.	Indirect Costs	Total
Year 2	41,000	500	7,000	0.0	8,775	57,275
Year 3						

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16. Other sources of financial support:

List financial support from all sources, including own institution, for this and related research projects.

CURRENTLY ACTIVE

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates
Epidemiology of Stroke	NINDS 5 R01-NS0 9695-03	\$65,569 (current year)	5/1/71 - 4/30/76
Private funds	Insurance Cos. 9,800 Industries 22,050 Individuals 4,403 36,253 (additional expenditures from reserve fund - same sources)	\$45,587 (amount expended)	1/1/73 - 12/31/73

PENDING OR PLANNED

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates

It is understood that the investigator and institutional officers in applying for a grant have read and accept the Council's "Statement of Policy Containing Conditions and Terms Under Which Project Grants Are Made."

Checks payable to:
Boston University

Mailing address for checks
Boston University School of Medicine
80 East Concord Street
Boston, Ma. 02118

Principal investigator

Typed Name Thomas R. Dawber, M.D., M.P.H.Signature _____ Date 1/25/74Telephone (617) 262-1400 6523
Area Code Number Extension

Responsible officer of institution

Typed Name Robert N. JordanTitle Assistant Treasurer -Boston University
Signature _____ Date 1/25/74Telephone (617) 262-4200 6101
Area Code Number Extension

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BIBLIOGRAPHY

Kannel, W. B. and Dawber, T. R.: The prudent management of the coronary-prone subject: coping with risk factors. In Russek, H.I. and Zohman, B.L. (eds.): Cardiovascular Therapy: the Art and the Science. Baltimore, Williams & Wilkins, 1971, pp. 225-236.

Dawber, T. R. and Kannel, W. B.: Current status of coronary prevention: lessons from the Framingham Study. Prevent. Med. 1: 499-512, Dec. 1972.

Kannel, W. B., and Dawber, T. R.: Atherosclerosis as a pediatric problem. J. Pediat. 80:544-554, Apr. 1972.

Kannel, W. B. and Dawber, T. R.: Contributors to coronary risk implications for prevention and public health: the Framingham Study. Heart and Lung 1:797-810, Nov.-Dec. 1972.

Kannel, W. B., Gordon, T., Wolf, P. A., and McNamara, P.: Hemoglobin and the risk of cerebral infarction: the Framingham Study. Stroke 3:409-420, July-Aug. 1972.

Dawber, T. R., Thomas, H. E., Jr., and McNamara, P. M.: Characteristics of the dicrotic notch of the arterial pulse wave in coronary heart disease. Angiology 24:244-255, Apr. 1973.

Wolf, P. A., Kannel, W. B., McNamara, P. M., and Gordon, T.: The role of impaired cardiac function in atherothrombotic brain infarction: the Framingham Study. Am. J. Pub. Health 63:52-58, Jan. 1973.

Kannel, W. B., and Dawber, T. R.: Hypertensive cardiovascular disease: the Framingham Study. In Onesti, G., Kim, K.E., and Moyer, J. H. (Eds.): Hypertension: Mechanisms and Management. New York, Grune & Stratton, 1973, pp. 93-110.

Margolis, J. R., Kannel, W. B., Feinleib, M., Dawber, T. R., and McNamara, P. M.: Clinical features of unrecognized myocardial infarction -- silent and symptomatic. Eighteen year follow-up the Framingham Study. Am. J. Cardiol. 32:1-7, July 1973.

Wolf, P. A., Dawber, T. R., Kannel, W. B., and Gordon, T.: Epidemiologic Assessment of the Stroke Candidate: the Framingham Study. Neurology 23:418, 1973 (Abstract)

Wolf, P. A., Kannel, W. B., McNamara, P. M., and Dawber, T. R.: The natural history of stroke: the Framingham Study. Circulation 48:49, 1973 (Abstract)

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Gresham, G. E., Fitzpatrick, T., Wolf, P. A., McNamara, P. M.,

Kannel, W. B., and Dawber, T. R.: The disability status of survivors of completed stroke in the Framingham Study.

Circulation 48:49, 1973 (Abstract)

Kannel, W. B., Wolf, P. A., and Dawber, T. R.: Current status of the epidemiology of atherothrombotic brain infarction: 1973 The Milbank Memorial Fund Quarterly, 1974 (In press).

Wolf, P. A.: Hypertension as a risk factor for stroke; proceedings of the ninth Princeton Conference on Cerebral Vascular Diseases, Princeton, N. J., Jan. 1974 (In press).

In preparation

Wolf, P. A., Kannel, W. B., Gordon, T., and Dawber, T. R.: The Stroke Profile: Epidemiologic Assessment of Risk of Stroke.

Wolf, P. A., Kannel, W. B., McNamara, P. M., and Dawber, T. R.: The natural history of stroke: the Framingham Study.

Wolf, P. A., McNamara, P. M., Gordon, T., Kannel, W. B., and Dawber, T. R.: Diabetes as a risk factor in stroke: the Framingham Study

Wolf, P. A., Kannel, W. B., McNamara, P. M., and Dawber, T. R.: Epidemiologic assessment of cigarette smoking in atherothrombotic brain infarction: the Framingham Study. Submitted for presentation to the American Academy of Neurology Meeting, San Francisco, Calif., April, 1974.

Dawber, T. R., et al: Coffee and Coronary Heart Disease. To be presented at the American College of Cardiology meeting, February 12, 1974.

Dawber, T. R., et al: Cigarette Smoking and Age in the Development of Myocardial Infarction - submitted to the American College of Physicians

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Bibliography (cont.)

Presentations:

Wolf, P. A.: The epidemiology of stroke -- tutorial at Harvard School of Public Health - March 1972

Wolf, P. A.: Profile of the potential stroke candidate: assessment of risk. Presented at the American Heart Symposium on Risk Factor Detection and Management, Dallas, Texas. (Nov. 1972)

Wolf, P. A.: Methods in chronic disease epidemiology: stroke. Presented to the Dept. of Epidemiology, McMaster Univ., Hamilton, Ontario - April 1973.

Wolf, P. A.: Epidemiological assessment of the stroke candidate: the Framingham Study. Presented at the 25th annual meeting of American Academy of Neurology, Boston, Ma. (April 1973)

Wolf, P. A.: Epidemiology of Stroke: the Framingham Study. Presented at Union Hospital, Fall River, Ma. (May 1973)

Wolf, P. A.: Rehabilitation in the brain damaged patient. Presented to the American Society of Law & Medicine, Inc., Boston, Ma. Sept. 1973

Wolf, P. A.: The natural history of stroke: the Framingham Study. Presented at the American Heart Association, Scientific Sessions, Atlantic City, N. J. (Nov. 1973)

Wolf, P. A.: Hypertension as a risk factor for stroke. Presented at the Ninth Princeton Conference on Cerebral Vascular Diseases, Princeton, N. J. (Jan. 1974)

Dawber, T. R.: Epidemiology and Natural History of Hypertension Presented at the annual meeting of the Georgia Heart Association in Atlanta, Georgia - September 1973.

Dawber, T. R.: Pooling Data -- Problems and Promises. Presented at a meeting of the American Gerontological Society, Miami, Florida, November 1973

Dawber, T. R.: "Framingham, Tecumseh, and Evans County" Presented at a meeting of the American College Health Association in April 1973.

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Projects for coming year

1. Use of vasculography in determining risk of coronary heart disease incidence
2. Cigar and pipe smoking vs. coronary heart disease risk
3. The effect of age in determining risk of coronary heart disease manifestations including myocardial infarction, sudden death and angina pectoris.
4. The relationship of cigarette smoking to risk of cerebro-vascular accidents.

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BOSTON UNIVERSITY MEDICAL CENTER -- FRAMINGHAM STUDY

Status of Exam 12

Cohort available for Exam 12	4,200
Subjects Examined	3,287
Subjects not examined	913
Deaths before exam (prior to 9/73)	124
Living subjects not examined	789
Incapacitated, living in Fram.*	76
Temporary refusal	37
Refusal*	214
Living out of Framingham area . .	103
No response to card mailed*	160
Whereabouts unknown*	151
No information	48

*4 additional deaths occurred after 9/1/73
1 from each category starred

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BOSTON UNIVERSITY MEDICAL CENTER -- FRAMINGHAM STUDY

CEREBROVASCULAR DISEASE REVIEW TO DATE (12/28/73)

	<u>ABI</u>		<u>C.E.</u>		<u>S.H.</u>		<u>I.H.</u>		<u>Other</u>		<u>T.I.A.</u> only		<u>Grand</u> <u>Total</u>	
<u>Exam</u>	<u>M.</u>	<u>W.</u>	<u>M.</u>	<u>W.</u>	<u>M.</u>	<u>W.</u>	<u>M.</u>	<u>W.</u>	<u>M.</u>	<u>W.</u>	<u>M.</u>	<u>W.</u>	<u>M.</u>	<u>W.</u>
1-11	66	79	17	17	10	13	6	5	4	3	9	8	112	125
													237	
12	11	11	1	2	1	5	3	5	4	3	4	4	20	22
	77	90	18	19	11	18	9	5	4	3	13	12	132	147
													279	
13	6	1	4	-	1	-	-	-	-	-	1	1		

ABI = Atherothrombotic brain infarct

(M = men)

C.E. = Cerebral embolus

W = women)

S.H. = Subarachnoid hemorrhage

I.H. = Intracerebral hemorrhage

T.I.A. = Transient ischemic attack

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INCIDENCE OF CORONARY HEART DISEASE

Exams 2 through 12

	<u>Exams 1 - 9</u>	<u>Exams 10 - 12</u>	<u>Total</u>
Coronary Heart Disease	580	342	922
Coronary Heart Disease other than Angina Pectoris	394	Not available	--
Angina Pectoris	347	188	535
Angina Pectoris, uncomplicated	231	Not available	--
Coronary Insufficiency plus ECG	85	48	133
Myocardial Infarction (ECG)	226	130	356
Myocardial Infarction History plus Transaminase	22	28	50
Coronary Heart Disease (Sudden Death)	84	51	135
Coronary Heart Disease (not sudden death)	88	86	174

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